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## Review

# Sodium-Glucose Cotransporter-2 inhibitors are potential therapeutic agents for treatment of non-diabetic heart failure patients



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## ABSTRACT

Despite recent developments in various therapies, heart failure remains a leading cause of morbidity and mortality worldwide. New pharmacological approaches are therefore needed to improve the outcomes of patients with heart failure. Diabetes mellitus is an important risk factor for heart failure, but until recently there had been no evidence that hypoglycemic agents prevent heart failure. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have now been shown to prevent cardiovascular events, especially hospitalization for heart failure, in three large randomized clinical trials: EMPA-REG OUTCOME, the CANVAS program, and the DECLARE-TIMI58 trial. It is expected, therefore, that SGLT2 inhibitors will be useful therapeutic agents for the treatment of heart failure. The DAPA-HF trial recently demonstrated that dapagliflozin significantly reduces cardiovascular death and hospitalization for heart failure in patients with heart failure with reduced ejection fraction (HFrEF). Importantly, these benefits of dapagliflozin were similarly observed in patients with or without diabetes, suggesting the drug's efficacy is independent of glycemic reduction. The results of that study highlight the significance of SGLT2 inhibition as a novel therapeutic approach to treating HFrEF, irrespective of the presence or absence of diabetes. Findings of the DAPA-HF trial may also challenge current assumptions about the mechanisms underlying the cardioprotective action of SGLT2 inhibitors. It is anticipated that ongoing clinical trials, mainly using dapagliflozin and empagliflozin, will provide further insight into the clinical importance of these drugs for the treatment of heart failure, including heart failure with preserved ejection fraction (HFpEF), and also the mechanisms underlying those clinical benefits.

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## Background

Despite recent progress in both pharmacological and non-pharmacological interventions, heart failure remains a leading cause of morbidity and mortality worldwide. Heart failure is caused by various cardiovascular diseases, often stemming from other illnesses. Diabetes mellitus, for example, is an important risk factor for cardiovascular disease, and the incidence of cardiovascular events is significantly higher in diabetic patients than in non-diabetic patients [1]. Heart failure is also one of the most common complications of type 2 diabetes mellitus (T2DM). Indeed, the incidence of heart failure among patients with T2DM is reportedly 2- to 5-fold greater than in the general population [2], and the risk of heart failure increases with an increase in HbA1c in T2DM patients [3]. Thus, in the treatment of T2DM, preventing the onset and progression of cardiovascular diseases that ultimately lead to heart failure is considered to be important. However, there has been no large-scale clinical study showing that tight glycemic control leads to early improvement in macrovascular outcomes in patients with T2DM. Moreover, no glucose-lowering agent has been clearly shown to prevent the onset or improve the outcomes of heart failure in patients with T2DM [4–6]. Until recently, heart failure had evidently been “the frequent, forgotten, and often fatal complication of T2DM” [7].

Against that background, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) demonstrated that empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, significantly reduced the incidence of cardiovascular events among T2DM patients [8]. In that study, the cardiovascular benefits of empagliflozin were manifested in particular as significant reductions in cardiovascular death and hospitalization for heart failure. Later, the Canagliflozin Cardiovascular Assessment Study (CANVAS) program and the Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI58) trial showed similar trends toward reducing hospitalization for heart failure, which suggests prevention of heart failure is a class effect for SGLT2 inhibitors. Based on those results, further exploration of the therapeutic potential of SGLT2 inhibitors on the outcomes of heart failure patients, irrespective of the presence or absence of T2DM, was expected. The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) reported in 2019 that dapagliflozin reduces the incidence of major cardiovascular events in patients with established heart failure with reduced ejection fraction (HFrEF) [9]. Importantly, it was also found that the magnitude of the benefit of dapagliflozin was similar in patients with or without T2DM.

In this review, we summarize the effects of SGLT2 inhibitors on cardiovascular outcomes derived from large-scale, randomized clinical trials, focusing especially on their beneficial effects on the prevention of heart failure onset and progression. We also describe what are thought to be likely mechanisms underlying the beneficial effects of SGLT2 inhibitors.

## Prevention of cardiovascular events, including heart failure, by SGLT2 inhibitors in patients with T2DM

Since 2008, the US Food and Drug Administration has required safety assessment for diabetes treatments, mandating large-scale clinical trials to prove that the treatment does not increase cardiovascular events. Consequently, the SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin have been the subject of several large-scale, randomized, clinical trials to prove their noninferiority to placebo for cardiovascular events. In addition

to their noninferiority, SGLT2 inhibitors exerted beneficial effects preventing cardiovascular events. The details of these clinical trials are summarized below.

### EMPA-REG outcome

This study was designed to compare the cardiovascular safety of the SGLT2 inhibitor empagliflozin with placebo during glucose-lowering therapy administered against a background of standard treatment to adults with T2DM who were at high cardiovascular risk. It was performed as a randomized, double-blind, placebo-controlled trial. A total of 7020 patients with T2DM (glycated hemoglobin level,  $\geq 7.0\%$  and  $\leq 9.0\%$ ), which included adults ( $\geq 18$  years of age) with an estimated glomerular filtration rate (eGFR) of at least 30 ml/min/1.73 m<sup>2</sup> of body-surface area and had established cardiovascular disease, were randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, which is the so-called 3-point major adverse cardiovascular events (MACE), as analyzed in the pooled empagliflozin group versus the placebo group. Primary composite outcomes occurred in 490 of the 4687 patients (10.5%) in the empagliflozin group and in 282 of the 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99;  $p = 0.04$  for superiority). In addition, the empagliflozin group had significant lower rates of death from any cause (5.7% vs. 8.3% in the placebo group; 32% risk reduction) and from cardiovascular causes (3.7% vs. 5.9%; 38% relative risk reduction). The empagliflozin group also had a significantly lower rate of hospitalization for heart failure (2.7% vs. 4.1%; 35% relative risk reduction). On the other hand, no significant differences were detected in the rates of myocardial infarction or stroke between the two groups.

Exploratory mediation analysis in this trial showed that changes in hematocrit and hemoglobin respectively mediated 51.8% and 48.9% of the effect of empagliflozin on the risk of cardiovascular death, indicating that changes in markers of plasma volume were the most important mediators of the reduction of cardiovascular death with empagliflozin [10].

### The CANVAS program

The CANVAS program integrated data from two trials, CANVAS and CANVAS-R, which involved a total of 10,142 participants with T2DM and high cardiovascular risk [11]. Participants in CANVAS were randomly assigned in a 1:1:1 ratio to receive canagliflozin at a dose of 300 mg, canagliflozin at a dose of 100 mg, or a matching placebo, while participants in CANVAS-R were randomly assigned in a 1:1 ratio to receive canagliflozin at an initial dose of 100 mg daily with an optional increase to 300 mg starting from week 12 or matching placebo. The total canagliflozin group contained 5795 participants, while the placebo group had 4347 participants. The primary outcome was 3-point MACE. Participants were men and women ( $\geq 30$  years of age) with T2DM (glycated hemoglobin level,  $\geq 7.0\%$  and  $\leq 10.5\%$ ) and eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup> of body surface area at entry. All participants also had a history of symptoms of atherosclerotic cardiovascular disease or risk factors for cardiovascular disease. In this study, risk factors were defined as T2DM for at least 10 years, systolic blood pressure  $> 140$  mmHg while receiving one or more antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or high-density lipoprotein (HDL) cholesterol level of less than 1 mmol/l (38.7 mg/dl). The numbers of participants with a history of cardiovascular disease were 3756 (64.8%) in canagliflozin group and 2900 (66.7%) in the placebo group. In this trial, therefore, 3486 (34%) participants who had cardiovascular risk factors, but not a

cardiovascular disease, were assessed for primary prevention of cardiovascular disease [11].

A total of 9734 participants completed the trial. Significantly fewer participants in the canagliflozin group than in the placebo group had a primary outcome event (3-point MACE): 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97;  $p < 0.001$  for noninferiority;  $p = 0.02$  for superiority). Superiority was not shown for the first secondary outcome in the testing sequence (death from any cause;  $p = 0.24$ ), and hypothesis testing was discontinued. Consequently, estimates for fatal secondary outcomes, including death from any cause (HR, 0.87; 95% CI, 0.74 to 1.01) or from cardiovascular causes (HR, 0.87; 95% CI, 0.72 to 1.06), are not considered to be significant. However, the results also showed that patients treated with canagliflozin had a lower risk of hospitalization for heart failure than patients who received placebo, which was similar to the results of EMPA-REG OUTCOME.

In addition, the results of a comparison between primary and secondary prevention were reported in 2018 [12]. The primary end point event rate was higher in the secondary prevention group than the primary prevention group (36.9 vs. 15.7/1000 patient-years,  $p < 0.001$ ). Among the total cohort, the primary endpoint was lower with canagliflozin than with placebo (26.9 vs. 31.5/1000 patients-years; HR, 0.86; 95% CI, 0.75–0.97;  $p < 0.001$  for no inferiority,  $p = 0.02$  for superiority), with no statistical evidence of heterogeneity (interaction  $p$ -value = 0.18) between the primary (HR, 0.98; 95% CI, 0.74–1.30) and secondary (HR, 0.82; 95% CI, 0.72–0.95) prevention cohorts. Regarding hospitalization for heart failure, there was no statistical evidence of heterogeneity between the primary and secondary prevention cohorts (interaction  $p$ -value = 0.91).

#### DECLARE-TIMI58

The DECLARE-TIMI58 trial included 17,160 patients ( $\geq 40$  years of age) with T2DM (glycated hemoglobin level,  $\geq 6.5\%$  and  $\leq 12.0\%$ ) with eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> of body surface area [13]. Eligible patients also had multiple risk factors for atherosclerotic cardiovascular disease (ASCVD) or had established ASCVD. Multiple risk factors (MRF) were being a man 55 years of age or older or a woman 60 years of age or older with one or more traditional risk factors, including hypertension, dyslipidemia (defined as a low-density lipoprotein cholesterol level  $>130$  mg/dl or the use of lipid-lowering therapy), or use of tobacco. These enrollment criteria suggest that many of the participants in this study were at lower risk than those in the EMPA-REG OUTCOME or the CANVAS program. This study included patients for both secondary (40.6%,  $n = 6974$ ) and primary (59.4%,  $n = 10,186$ ) prevention of cardiovascular diseases. The ratio of patients for primary prevention of cardiovascular diseases within the total participants in the study was higher than in two previously discussed studies.

The patients were randomly assigned to receive 10 mg of dapagliflozin ( $n = 8582$ ) or placebo ( $n = 8578$ ). The primary safety outcome was 3-point MACE. The primary efficacy outcomes were 3-point MACE and a composite of cardiovascular death or hospitalization for heart failure. This is the first trial using SGLT2 inhibitors in which hospitalization for heart failure was included in a primary endpoint. Secondary efficacy outcomes were a renal composite ( $\geq 40\%$  decrease in eGFR to  $<60$  ml/minute/1.73 m<sup>2</sup> of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

The 17,160 participants included 10,186 without ASCVD who were followed for a median of 4.2 years. In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of

the 95% CI,  $<1.3$ ;  $p < 0.001$  for noninferiority). In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR, 0.93; 95% CI, 0.84 to 1.03;  $p = 0.17$ ). However, dapagliflozin did result in a lower rate of cardiovascular death or hospitalization for heart failure than placebo (4.9% vs. 5.8%; HR, 0.83; 95% CI, 0.73–0.95;  $p = 0.005$ ). This reflected a lower rate of hospitalization for heart failure (HR, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (HR, 0.98; 95% CI, 0.82 to 1.17). This efficacy of dapagliflozin for cardiovascular death or hospitalization for heart failure was similar in the subgroup of patients with established ASCVD (7.8% in the dapagliflozin group and 9.3% in the placebo group; HR, 0.83; 95% CI, 0.71–0.98) and in the subgroup of patients with MRF for primary prevention (2.8% in the dapagliflozin group and 3.4% in the placebo group; HR, 0.84; 95% CI, 0.67–1.04;  $p = 0.99$  for interaction).

A sub-analysis of the impact of baseline left ventricular ejection fraction (LVEF) on the clinical benefit of dapagliflozin was recently published by Kato et al. [14]. Of the 17,160 participants in the DECLARE-TIMI 58 trial, 671 (3.9%) with HFrEF, 1316 (7.7%) with heart failure with preserved EF (HFpEF), and 15,173 (88.4%) had no history of heart failure at baseline. Dapagliflozin also reduced cardiovascular death or hospitalization for heart failure more in patients with HFrEF (HR 0.62, 95% CI, 0.45–0.86) than in those with HFpEF (HR, 0.88; 95% CI, 0.76–1.02;  $p$ -interaction 0.046). Dapagliflozin reduced hospitalization for heart failure in those with HFrEF (HR, 0.64; 95% CI, 0.43–0.95) and with HFpEF (HR, 0.76; 95% CI, 0.62–0.92) [14]. Moreover, a recent analysis revealed that dapagliflozin consistently reduced the risk of atrial fibrillation and atrial flutter (AF/AFL) events (HR, 0.81; 95% CI, 0.68–0.95,  $p = 0.009$ ), irrespective of the presence or absence of a history of AF/AFL at baseline [15]. The presence of ASCVD versus MRF, or a history of heart failure did not modify the reduction in AF/AFL events observed with dapagliflozin [15].

Zelniker et al. reported a meta-analysis of all three trials of SGLT2 inhibitors described above, in which a total of 34,322 patients (60.2% with established ASCVD) were analyzed [16]. SGLT2 inhibitors reduced MACE by 11% (HR, 0.89; 95% CI, 0.83–0.96;  $p = 0.0014$ ), with benefit seen only in patients with ASCVD; no benefit was seen in those with MRF. On the other hand, SGLT2 inhibitors also reduced the risk of the composite of cardiovascular death or hospitalization for heart failure by 23% (HR, 0.77; 95% CI, 0.71–0.84;  $p < 0.0001$ ) with similar benefits in those with or without ASCVD. The effect on hospitalization for heart failure alone was particularly robust, with a 31% reduction in relative risk among all patients (HR, 0.69; 95% CI, 0.61–0.79;  $p < 0.0001$ ), a 29% reduction in relative risk in the ASCVD group for secondary prevention (HR, 0.71; 95% CI, 0.62–0.82;  $p < 0.0001$ ), and a 36% reduction in relative risk in the MRF group for primary prevention (HR, 0.64; 95% CI, 0.48–0.85;  $p = 0.0021$ ) [16].

#### SGLT2 inhibition as a novel therapeutic approach to HFrEF – the DAPA-HF trial –

The three landmark trials discussed above show the prevention of heart failure onset by SGLT2 inhibitors in T2DM patients at high cardiovascular risk, which raises a question as to whether these agents improve clinical outcomes in patients with heart failure, irrespective of the absence or presence of T2DM.

DAPA-HF, a large-scale, placebo-controlled, randomized clinical trial of SGLT2 inhibitors for HFrEF, answered that question. In this study, 4744 patients with New York Heart Association (NYHA) class II, III, or IV heart failure, EF  $\leq 40\%$ , and eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup> were enrolled and received either dapagliflozin (at a dose of 10 mg once daily) or placebo in addition to the required standard devices and drug therapy for heart failure. Among these patients were



1096 Asian participants (343 Japanese participants). Non-diabetic patients accounted for 58.2% of the participants, 96% were taking a  $\beta$ -blocker, 71% had MRA. The principal cause of the heart failure was ischemia in 55.5%, while the cause was nonischemic in 36.1%. LVEF was  $31.2 \pm 6.7\%$ , median N-terminal prohormone B-type natriuretic peptide (NT-proBNP) was 1428 (857–2655) pg/ml, and 67.7% were NYHA class II. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

The primary outcome occurred in 386 of the 2373 patients (16.3%) in the dapagliflozin group and in 502 of the 2731 patients (21.1%) in the placebo group (HR, 0.74; 95% CI, 0.65–0.85;  $p < 0.001$ ). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (HR, 0.70; 95% CI, 0.59–0.83). Adverse events included major hypoglycemia (0.2% in both the dapagliflozin and placebo groups), amputation (0.5% vs. 0.5%), and diabetic ketoacidosis (0.1% vs. 0%). There was no notable excess of any event in the dapagliflozin group.

The effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups, including patients without T2DM at baseline (with T2DM HR, 0.75; CI 0.63–0.90, without T2DM HR, 0.73; CI, 0.57–0.88). The patients in NYHA functional class III or IV appeared to receive less benefit than those in class II. However, findings with other subgroups that also reflected more advanced disease (e.g. more reduced EF, poorer renal function, and higher NT-proBNP level) were not consistent with the finding for NYHA class. It will be necessary to wait for further evaluation to clarify which patient conditions are more affected by administration of a SGLT2 inhibitor and the reasons.

Another small clinical trial of dapagliflozin for heart failure patients was reported recently. The DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction) trial was a multicenter, randomized, controlled trial of heart failure patients with LVEFs  $\leq 40\%$ , NYHA classes II–III, eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>, and elevated natriuretic peptides [17]. The 263 enrolled patients were randomized to dapagliflozin 10 mg daily or placebo groups for 12 weeks. The two primary outcomes were (1) mean NT-proBNP and (2) the proportion of patients with a  $\geq 5$ -point increase in heart failure disease-specific health status on the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall symptom score or a  $\geq 20\%$  decrease in NT-proBNP. In this study, there was no significant difference in NT-proBNP levels between the dapagliflozin and placebo groups. However, for the other primary outcome, the dapagliflozin group showed significant improvement as compared to the placebo group [17].

Both these trials strongly suggest a SGLT2 inhibitor has beneficial effects in patients of HFrEF, irrespective of their diabetic status. The finding that dapagliflozin is as effective in patients without T2DM as in those with the disease suggests the beneficial effects of SGLT2 inhibitors on heart failure are exerted through mechanisms other than those reflecting improvement of metabolic disorders specific to T2DM, such as lowering of blood glucose. Further evaluation of the mechanisms underlying the beneficial effects of SGLT2 inhibitors on patients with HFrEF is necessary. At present, several other clinical trials are underway to validate the efficacy of SGLT2 inhibitors in heart failure patients, including those with HFpEF. The trial names and their overviews are listed in Table 1. The information obtained from these studies may provide the impetus to change the treatment of heart failure in the near future.

### Mechanisms thought likely to underlie the cardioprotective effects of SGLT2 inhibitors

In the DAPA-HF study, the reductions in cardiovascular death and hospitalization for heart failure in the dapagliflozin group

were observed in patients with or without T2DM. This suggests the beneficial effects of SGLT2 inhibitors on heart failure patients are mediated by mechanisms other than glycemic reduction and correction of T2DM-related metabolic disorder. The mechanisms currently thought likely to underlie the cardioprotective effects of SGLT2 inhibitors are described below (Fig. 1).

### Blood pressure reduction and diuresis

Two major factors contributing to the cardioprotective effects of SGLT2 inhibitors are their blood pressure lowering and diuretic effects. The primary effects of SGLT2 inhibition are reductions in glucose and Na<sup>+</sup> reabsorption in the proximal tubule. Most likely both the natriuresis and the osmotic effect of glucosuria are involved in the diuretic effect of SGLT2 inhibitors with a resultant contraction of plasma volume [18]. The natriuresis induced by SGLT2 inhibitors is thought to be transient, but the decreases in systolic (5–6 mmHg) and diastolic (1–2 mmHg) blood pressure are sustained, as was shown in the EMPA-REG OUTCOME [8].

It is also known that blood pressure is closely related to the onset of heart failure. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) was a randomized, double-blind, active-controlled clinical trial [19]. This trial enrolled 33,357 participants with hypertension and high cardiovascular disease risk to compare the efficacies of antihypertensive drugs, including chlorthalidone, amlodipine, lisinopril, and doxazosin, against coronary heart disease. As a secondary outcome, the chlorthalidone group had a lower 6-year rate of heart failure than either the amlodipine or lisinopril group. Further analysis in the Heart Failure Validation Study of ALLHAT [20] revealed that chlorthalidone reduced the risk of HFrEF to a significantly greater degree than amlodipine or doxazosin, but had an effect similar to lisinopril. In addition, chlorthalidone also reduced the risk of HFpEF significantly more than amlodipine, lisinopril, or doxazosin. These results demonstrated that chlorthalidone, which has antihypertensive and diuretic effects, prevents heart failure without distinguishing between HFrEF and HFpEF.

The blood pressure lowering and diuretic effects of SGLT2 inhibitors may also contribute to the prevention of heart failure. With respect to the diuretic effect of SGLT2 inhibitors, a difference from the effect of loop diuretics has been suggested. In a mathematical model, dapagliflozin produced a 2-fold greater reduction in interstitial fluid volume than blood volume, while bumetanide, a loop diuretic, reduced interstitial volume by only 78% of the reduction in blood volume, suggesting the interstitial-dominant volume reducing effect of SGLT2 inhibitors may mediate their beneficial effects preventing heart failure [21,22].

A randomized trial of intensive versus standard blood-pressure control (SPRINT) [23] showed that among patients at high risk for cardiovascular events, targeting a systolic blood pressure of  $<120$  mmHg as compared to  $<140$  mmHg resulted in significantly lower rates of cardiovascular events, predominantly a lower incidence of heart failure. In the EMPA-REG OUTCOME, CANVAS program, and DECLARE-TIMI 58 trial, systolic blood pressures in the patients' background profiles were around 130–140 mmHg, and they were lowered by about 5 mmHg by the SGLT2 inhibitor. This blood pressure lowering effect may contribute to the suppression of cardiovascular events, especially the incidence of heart failure.

In animal experiments, ipragliflozin, reportedly prevented LV hypertrophy and fibrosis in non-diabetic obese rats with hypertension (DS/obese rat) without affecting plasma glucose levels [24]. Treatment of ipragliflozin ameliorated LV hypertrophy, and changes in LV wall thickness and fibrosis in association with

**Table 1**

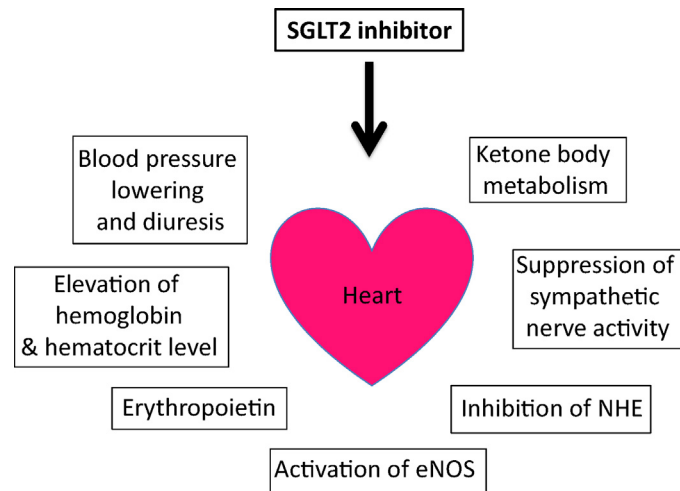
Ongoing outcome clinical trials of SGLT2 inhibitors for patients with heart failure.

Drug	Trial name	Treatment arm	HFpEF or HFrEF	Inclusion criteria	Estimated enrollment number	Primary endpoint	Estimated study completion date
Dapagliflozin	DELIVER	Dapagliflozin vs. placebo	HFpEF	Age $\geq$ 40 years, NYHA class II–IV, and medical history of typical symptoms/signs of heart failure $\geq$ 6 weeks, LVEF $>$ 40% and evidence of structural heart disease, elevated NT-proBNP levels, patients currently hospitalized for HF, must be off intravenous HF medications for at least 24 h, etc.	4700	Time to the first occurrence of any of the components of CV death, hospitalization for HF or urgent HF visit	2021/6/22
	DETERMINE-preserved	Dapagliflozin vs placebo	HFpEF	Age $\geq$ 40 years, LVEF $>$ 40% and evidence of structural heart disease, elevated NT-proBNP levels, patients should receive background standard of care, etc.	500	Change from baseline in 6MWD at week 16, change from baseline in KCCQ-TSS at week 16	2020/7/3
	DETERMINE-reduced	Dapagliflozin vs placebo	HFrEF	Age $\geq$ 18 years, NYHA class II–IV for at least 8 weeks, LVEF $\leq$ 40% and evidence of structural heart disease, elevated NT-proBNP levels, etc.	313	Change from baseline in 6MWD at week 16	2020/2/26
Empagliflozin	EMRIRE-HF	Empagliflozin vs placebo	HFrEF	Age $\geq$ 18 years, optimal heart failure therapy, LVEF $\leq$ 0.40, eGFR $>$ 30 ml/min/1.73 m <sup>2</sup> , BMI $<$ 45 kg/m <sup>2</sup> , NYHA class I–III, etc.	190	Between-group difference in the change of plasma concentration of NT-proBNP	2020/1/17
	EMPEROR-preserved	Empagliflozin vs placebo	HFpEF	Age $\geq$ 18 years, NYHA class II–IV for at least 8 weeks, LVEF $>$ 40%, elevated NT-proBNP levels, structural heart disease within 6 or documented HHF within 12 months, etc.	5750	Time to first event of CV death or HHF in patients	2020/11/9
	EMPEROR-reduced	Empagliflozin vs placebo	HFrEF	Age $\geq$ 18 years, NYHA class II–IV, LVEF $\leq$ 40%, elevated NT-proBNP levels, etc.	3730	Time to first event of CV death or HHF in patients	2020/7/20
	EMPA-VISION	Empagliflozin vs placebo	HFpEF and HFrEF	Age $\geq$ 18 years, NYHA class II–IV. Cohort A; HFrEF, appropriate dose of medical therapy for HF. Cohort B HFpEF, elevated NT-proBNP, structural heart disease (LA enlargement and/or LVH) by echo, Elevated NT-proBNP, etc.	86	Change from baseline to week 12 in PCr/ATP ratio in the resting stage measured by <sup>31</sup> P-MRS.	2020/5/29
	EMPERIAL-preserved	Empagliflozin vs placebo	HFpEF	Age $\geq$ 18 years, NYHA class II–IV, chronic HF with preserved EF defined as LVEF $>$ 40%, elevated NT-proBNP, structural heart disease documented by echo, and/or documented hospitalization for heart failure within 12 months, etc.	315	Change of 6MWD from baseline to week 12	2019/10/9
	EMPERIAL-reduced	Empagliflozin vs placebo	HFrEF	Age $\geq$ 18 years, NYHA class II–IV, chronic HF with reduced EF defined as LVEF $\leq$ 40%, etc.	312	Change of 6MWD from baseline to week 12	2019/10/7
	EMPULSE	Empagliflozin vs placebo	HFpEF and HFrEF	Age $\geq$ 18 years, currently hospitalized for the primary diagnosis of acute heart failure, patients must be randomized after at least 25 h and no later than days after admission, elevated NT-proBNP levels, etc.	500	Composite endpoint composed of time to death, number of heart failure events (HFEs), time to first HFE, change in KCCQ-CCS from baseline after 90 days of treatment	2021/7/3
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; CV death, cardiovascular death; 6MWD, 6-minute walking distance; KCCQ-TSS, Kansas-City Cardiomyopathy Questionnaire-Total Symptom Score; eGFR, estimated glomerular filtration ratio; HHF, hospitalization for heart failure; BMI, body mass index; PCr, phosphocreatine; MRS, magnetic resonance spectroscopy; KCCQ-CCS, Kansas-City Cardiomyopathy Questionnaire-Clinical Summary Score.							

increased urine volume. In the ipragliflozin-treated group, systolic blood pressure was lower than in the DS/obese control group at 11 weeks of age, without a significant difference in blood glucose, insulin, or lipid levels; body weights; or heart rate.

#### Ketone body metabolism

A number of studies have reported that ketone levels are elevated in T2DM patients treated with a SGLT2 inhibitor, although



**Fig. 1.** Mechanisms thought to underlie the cardioprotective effects of SGLT2 inhibitors.  
**eNOS**, endothelial nitric oxide synthase; **NHE**,  $\text{Na}^+/\text{H}^+$  exchanger; **SGLT2**, sodium-glucose cotransporter-2.

the mechanism is not completely clear [25–30]. In addition, several reports have shown that cardiac uptake of ketone bodies is significantly increased in patients with heart failure [31]. We therefore suggest that SGLT2 inhibitors improve myocardial fuel metabolism and cardiac efficiency by shifting fuel utilization away from lipids and glucose to ketone bodies.

Nearly 95% of myocardial energy is derived from mitochondrial oxidative metabolism and ~5% from glycolysis and guanosine-5'-triphosphate formation [32]. In the normal heart, fatty acids (~60–70%) and glucose (~30%) are the major energy substrates [33], but the heart can also take up and oxidize ketone bodies ( $\beta$ -hydroxybutyrate and acetoacetate) [33]. Plasma ketone bodies are formed from fatty acids in the liver. Their concentration in arterial plasma is normally very low, making them only a minor substrate in the myocardium. Metabolic flexibility refers to the ability of cardiac muscle to switch between free fatty acids and glucose as the predominant fuel source based on substrate availability [32]. During starvation or poorly controlled diabetes, the liver converts free fatty acids to the ketone bodies, such as acetoacetate and  $\beta$ -hydroxybutyrate, elevating plasma ketone body concentrations secondary to low insulin and high fatty acids, and they become a major substrate for the myocardium [33].

Ketone bodies serve as an alternative fuel and play a critical role in human survival during periods of starvation, providing fat-derived calories to the brain, heart, kidneys, and other vital tissues. An advantage of ketone bodies is that more ATP is produced per molecule of oxygen consumed than with glucose or free fatty acids, which increases cardiac efficiency [32]. In the setting of the failing heart, the myocardium is unable to optimally use canonical fuel. Cardiac uptake of carbohydrate (glucose, lactate, and pyruvate) is decreased, whereas uptake of total ketone bodies and  $\beta$ -hydroxybutyrate are increased, in diabetics as compared to non-diabetics [34]. Moreover, there is a significant correlation between the plasma BNP levels and cardiac uptake of total ketone bodies, which suggests cardiac utilization of ketone bodies increases with deterioration of LV function [34]. In addition, myocardial ketone body utilization is preserved in advanced heart failure, although skeletal-muscle ketone body utilization is impaired [35]. These reports support the idea that increases in the plasma ketone body concentration induced by SGLT2 inhibitors may protect failing hearts in diabetic patients. However, further evaluation is needed to clarify whether the protective effect of ketone bodies underlies the cardioprotective effects of SGLT2 inhibitors in non-diabetic patients with HFrEF. It also should be clarified whether the

increase in ketone bodies contributes to the prevention of HFpEF in patients with T2DM.

Ketone bodies not only serve as an energy source, they also have several functions related to intracellular signaling. For example,  $\beta$ -hydroxybutyrate is known to be an endogenous inhibitor of histone deacetylases (HDACs). These enzymes affect the acetylation status of histones and other important cellular proteins, thereby playing an important role in the regulation of gene expression. They are also recognized to be potentially useful therapeutic targets in various human disorders, including pathological cardiac remodeling [36]. Lkhagva et al. [37] reported that HDAC inhibition improves cardiac function, reducing chamber size, improving cardiac metabolism, and reducing inflammation in failing rat hearts. It may be that HDAC inhibition by  $\beta$ -hydroxybutyrate leads to improved signaling in heart failure. It is noteworthy, however, that cardiac-specific deletion of HDAC1 and 2 in developing mice is neonatally lethal due to cardiac arrhythmias, dilated cardiomyopathy, and up-regulation of genes encoding skeletal muscle-specific contractile proteins and  $\text{Ca}^{2+}$  channels [38].

$\beta$ -hydroxybutyrate is also reported to be a ligand for G protein-coupled receptor 41 (GPR41), which is also known as free fatty acid receptor 3 (FFAR3). GPR41 is highly expressed within sympathetic ganglia, and its inhibition by  $\beta$ -hydroxybutyrate reportedly suppresses sympathetic nervous system activity and heart rates [39]. This suggests ketone bodies directly regulate sympathetic nerve activity, thereby controlling energy expenditure used to maintain metabolic homeostasis. In addition, the crucial role played by the sympathetic nervous system in the development of heart failure suggests SGLT2 inhibitor-induced increases in  $\beta$ -hydroxybutyrate may improve heart failure status by modulating sympathetic nerve activity.

#### Sodium-hydrogen exchanger

Recent studies suggest that SGLT2 inhibitors may reduce intracellular  $\text{Na}^+$  load in failing cardiomyocytes by inhibiting the sarcolemmal  $\text{Na}^+/\text{H}^+$  exchanger (NHE) [18]. Because most studies have shown that SGLT2 is not expressed in rodents [40] or in human hearts, whether the subjects were healthy or suffered from a pathological condition [41], it is not thought that SGLT2 inhibitors act directly on cardiac myocytes. Recently, however, empagliflozin was observed to directly modify cytoplasmic  $\text{Na}^+$  and  $\text{Ca}^{2+}$  concentrations and the mitochondrial

$\text{Ca}^{2+}$  concentration in isolated ventricular myocytes from rabbits and rats by impairing NHE activity [42]. This effect was independent of SGLT2 inhibition. NHE expression is increased in heart failure, which appears to increase conversion of pyruvate to lactate, leading to intracellular acidosis [18]. Elevated cytoplasmic  $\text{Na}^+$  enhances mitochondrial  $\text{Ca}^{2+}$  extrusion, as mitochondrial  $\text{Ca}^{2+}$  is exported from mitochondria into the cytosol via the cytosolic  $\text{Na}^+/\text{Ca}^{2+}$  exchanger. The mitochondrial  $\text{Ca}^{2+}$  concentration is important not only for ATP production, but also for preserving mitochondrial anti-oxidative capacity [18]. A similar effect was shown for dapagliflozin and canagliflozin in mouse cardiomyocytes and perfused mouse hearts, suggesting this is a class effect of SGLT2 inhibitors [43]. Several reports have demonstrated that decreasing the intracellular  $\text{Na}^+$  concentration through NHE inhibition has a cardioprotective effect [44,45]. Thus, SGLT2 inhibitors may exert a protective effect by directly acting on the myocardium through inhibition of NHE, without depending on SGLT2 inhibition.

#### *Elevation of hemoglobin and hematocrit levels and erythropoietin*

Treatment with an SGLT2 inhibitor leads to a modest increase in hematocrit (2–4%) compared to placebo [46]. The increased urinary volume induced by SGLT2 inhibitors returns to baseline within 1 week, but the elevated hematocrit continues to increase over 2 months [46]. In a study comparing the effects of dapagliflozin and hydrochlorothiazide on hematocrit after 12 weeks, it was found that hematocrit was increased by 2.2% (95% CI, 1.3% to 3.0%) in the dapagliflozin group, whereas it was changed by −0.9% (95% CI, −2.3% to +0.6%) in the hydrochlorothiazide group [47]. This suggests the change in hematocrit induced by SGLT2 inhibitors is not explained solely by hemoconcentration due to diuresis. Indeed, increases in erythropoietin levels have been reported after treatment of SGLT2 inhibitors. Lambers Heersping et al. reported that serum erythropoietin levels are transiently increased from baseline in the dapagliflozin group up to week 4 of administration, followed by a gradual decline until week 12 [47]. In another trial, in which 6 months of empagliflozin treatment was associated with a significant reduction in the LV mass index, erythropoietin levels were significantly increased after 1 month of empagliflozin treatment as compared to placebo (adjusted mean difference at 1 month 3.86 mIU/ml; 95% CI, 0.99 mIU/ml to 6.74 mIU/ml,  $p < 0.05$ ; at 6 months 1.91 mIU/ml; 95% CI, −0.96 mIU/ml to 4.78 mIU/ml) [48]. It was also reported that empagliflozin treatment was associated with an early increase in plasma erythropoietin levels accompanied by an increase in hematocrit in people with T2DM and coronary artery disease [48]. Erythropoietin is produced by “neural crest-derived” fibroblasts residing near the proximal tubules in the kidney [46]. Selective proximal tubule injury induces transdifferentiation of erythropoietin-producing fibroblasts into myofibroblasts, resulting in a reduction in erythropoietin production [49]. Reabsorption of  $\text{Na}^+$  with glucose via SGLT2 in the proximal tubular epithelial cells is followed by consumption of ATP for  $\text{Na}^+/\text{K}^+$  ATPase, which extrudes  $\text{Na}^+$  by replacing it with  $\text{K}^+$ . Excess  $\text{Na}^+$  absorption via SGLT2 observed in T2DM may promote a hypoxic state and deterioration of the proximal tubules. SGLT2 inhibitors suppress  $\text{Na}^+$  reabsorption, reduce ATP consumption by  $\text{Na}^+/\text{K}^+$  ATPase, and improve relative hypoxic conditions in the proximal tubules. This may allow reversion of myofibroblasts to erythropoietin-producing fibroblasts, resulting in enhancement of hematopoiesis [46]. In the DAPA-HF trial, the beneficial effects of dapagliflozin on the outcomes of heart failure patients were similar in patients with or without T2DM. In that trial, hematocrit levels were increased by about 2% in the dapagliflozin group [9],

which may reflect dapagliflozin-induced elevation of erythropoietin levels.

It should be noted, however, that erythropoiesis-stimulating agents (ESAs) have failed to improve clinical outcomes in heart failure. The effects of ESAs on heart failure outcomes were examined in the RED-HF (Reduction of Events by Darbepoetin Alfa in Heart Failure) trial, in which 2278 patients were enrolled [50]. Median hemoglobin levels were increased, but no beneficial effect of ESA was observed on the primary composite endpoint of death and hospitalization with worsening heart failure or any of the other endpoints. To the contrary, ischemic stroke and embolic/thrombotic events were increased in the ESA group [51]. But because the increase in endogenous erythropoietin levels with administration of a SGLT2 inhibitor may differ from the increase elicited by exogenous administration of ESA, the possibility that the cardioprotective effects are mediated via SGLT2 inhibitor-induced erythropoietin cannot be excluded. Further examination is needed to verify the contribution of increased erythropoietin and enhanced hematopoiesis to the cardioprotective effects induced by SGLT2 inhibition.

#### *Sympathetic nerve activity*

Despite the reductions in blood pressure and plasma volume, heart rate was also decreased somewhat in the empagliflozin group in EMPA-REG OUTCOME. In a subanalysis of three placebo-controlled, double-blind studies of luseogliflozin, treatment with luseogliflozin elicited significant reductions in heart rate from baseline in patients with relatively high heart rates [52]. We therefore suggest that SGLT2 inhibitors suppress sympathetic nerve activity. Activation of the sympathetic nervous system is closely related to the onset and progression of heart failure. In addition,  $\beta$ -blockers are standard therapy for patients with HFrEF. The suppressive effect of SGLT2 inhibitors on sympathetic nerve activity may thus be protective in failing hearts. The mechanism by which SGLT2 inhibitors suppress sympathetic nerve activity is not yet fully understood, although one possible explanation is described above in the section on “Ketone body metabolism.”

#### *Activation of endothelial nitric oxide synthase*

Acute canagliflozin treatment significantly reduced myocardial infarct size, serum troponin-T levels, and LV dysfunction in a non-diabetic mouse myocardial ischemia/reperfusion injury model [53]. Canagliflozin also significantly increased endothelial nitric oxide synthase (eNOS) during ischemia/reperfusion, thereby enhancing endothelium-dependent vasodilation [53]. In addition, empagliflozin ameliorated high glucose-induced increases in endothelial cell senescence markers and oxidative stress, and decreased eNOS expression and nitric oxide formation [54]. These effects of SGLT2 inhibitors on endothelium-dependent vasodilation and eNOS activity may contribute to their cardioprotective efficacy.

#### **Conclusion**

The beneficial effects of SGLT2 inhibitors preventing macrovascular events and hospitalization for heart failure were shown in three landmark trials; EMPA-REG OUTCOME, the CANVAS program, and the DECLARE-TIMI58 trial. More recently, the DAPA-HF trial, which showed that dapagliflozin significantly improved the outcomes of patients with HFrEF, irrespective of the presence or absence of T2DM, demonstrated the significance of SGLT2 inhibitors as novel therapeutic agents in heart failure. We anticipate that further research will provide additional insight into the clinical importance of these drugs to the treatment of heart failure, including both HFpEF



and acute decompensated heart failure, as well as the mechanisms underlying their clinical benefits.

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